IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: PATENT APPLICATION of
Inventor(s) SHERMAN, et al.

Appln. No.: 09/544,108 Group Art Unit: 1648

Filed: April 6, 2000 Examiner: Brown, T.

Title: COMPOSITION AND METHOD OF TREATING HEPATITIS C

DECLARATION UNDER 37 CFR § 1.132

Hon. Commissioner of Patents
and Trademarks
PO Box 1450
Alexandria, VA 22313

Sir:

Kenneth Sherman, MD, PhD of Cincinnati, Ohio declares as follows:

1. I am a named inventor of the subject matter of the above-identified patent application.
2. I am a national and international authority in the diagnosis and management of viral hepatitis.
3. I received my undergraduate training and a PhD in Microbiology (Virology) from Rutgers University.
4. I did my postdoctoral fellowship included training in Epidemiology and Study Design at the Transmissible Disease Laboratory of the American Red Cross National Blood Center in Bethesda, Maryland.
5. I graduated from the George Washington University School of Medicine in 1985 and subsequently obtained residency training in Internal Medicine in Hawaii.
6. I subsequently trained in Hepatology and Gastroenterology, including liver Transplantation at Fitzsimmons Army Medical Center and the University of Colorado Health Sciences Center.
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9. My laboratory focuses on genetic variability of the hepatitis C virus in immunosuppressed populations.
10. We evaluated the addition of thymosin alfa-1 (TA1), an immunomodulatory peptide, to the standard interferon (IFN) treatment regimen for hepatitis C to determine if combination therapy shows biological activity using outcome measures including normalization of alanine aminotransferase levels, histological activity, and viral load during treatment. We performed a randomized, double-blind, placebo-controlled trial to compare the biological activity of a combination TA1 and IFN with that seen for IFN alone in patients with chronic hepatitis C infection. One hundred nine patients were randomized for intention to treat and received 1.6 mg of TA1 subcutaneously twice weekly and 3 MU of IFN three times weekly; 3 MU of IFN three times weekly and placebo TA1; or placebo for both agents. All patients had chronic HCV infection with confirmation of chronic hepatitis on liver biopsy. Biochemical responders were followed up until alanine aminotransferase (ALT) levels became abnormal or for 26 weeks, and relapsers were retreated for 26 weeks in the same treatment arm. One hundred three patients completed treatment for 26 weeks, and six patients dropped out. The groups were similar with regard to sex, gender distribution, baseline histological activity index (HAI) score, risk factors, and viral titers.
11. End-of-treatment biochemical response was seen in 37.1% of patients treated with combination therapy, 16.2% of patients treated with IFN alone, and 2.7% of untreated controls by intent-to-treat analysis (IFN/TA1 vs. IFN, x2 5 4.05, P 5 .04). HCV RNA clearance was seen in 37.1% of IFN/TA1-treated patients and 18.9% of IFN-treated subjects. Mean HCV RNA titers were significantly lower than baseline at weeks 8, 16, and 24 after drug initiation among patients treated with IFN/TA1 but not in the other treatment arms. Histological improvement, as evidenced by a decrease in HAI of more than two points, occurred in the combination therapy arm more frequently than in comparison groups. Cumulative sustained biochemical responses were 14.2% and 8.1% in the IFN/TA1 and IFN arms, respectively, based on an intention-to-treat model. The combination of TA1 and standard IFN treatment for chronic hepatitis C showed evidence of biological activity at the completion of treatment by biochemical, histological, and virological outcome measures.
12. The following are figures and tables that were a part of this study.

The active randomization set is shown in Table 1. These groups were statistically similar with respect to gender distribution, race distribution baseline ALT levels, pretreatment HCV RNA titer, risk factor distribution and prevalence of cirrhosis.

TABLE 1. Pretreatment Patient Demographics by Randomization Group

	IFN/TA1 (n = 35)	IFN (n = 37)	Placebo (n = 37)	P
Age (yr)*	45 ± 1.9	38 ± 1.2	41 ± 1.7	<.01
Male:Female	27:8	27:10	31:6	NS
Race White:Other	27:8	26:11	22:15	NS
Risk factors				NS
Intravenous drug abuse	3	2	9	
Transfusion	7	5	7	
Tattoos	3	8	7	
Combination	5	2	2	
Unknown	17	20	12	
ALT ± SEM*	137 ± 11.1	154 ± 22	189 ± 26	NS
HCV RNA ($\times 10^6$ Eq/ml)*†	9.09 ± 1.9	6.0 ± .99	11.12 ± 1.8	NS
HAI	10.32	10	9.43	NS
Cirrhosis	2	2	3	NS
Prior interferon therapy	3	1	0	NS

*Mean ± SEM.

†HCV RNA titer based on Quantiplex bDNA assay. No. of patients with titers $<3.5 \times 10^6$ Eq/mL: IFN/TA1, 1; IFN, 3; placebo, 2.

The overall distribution of genotypes is shown in Fig. 1. Although genotype 1 was significantly more prevalent than other types, there were no significant differences within treatment arms for each type.

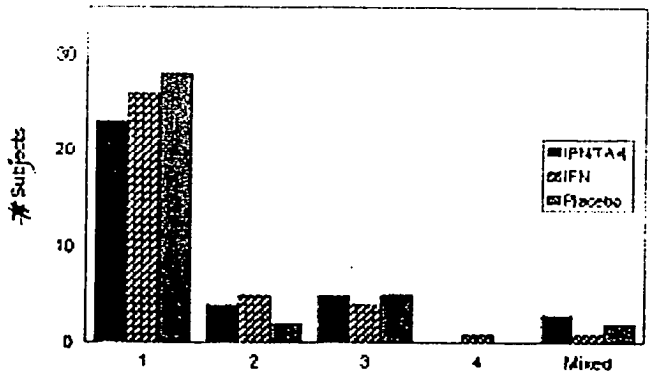

FIG. 1. Distribution of genotypes according to treatment randomization group. Genotypes are identified by hybridization technique and serological typing method. There are no statistically significant differences in distribution by randomization group.

By intention to treat analysis end of treatment results are shown in Table 2.

TABLE 2. ETR Based on Intention-to-Treat Model

Treatment Arm	Biochemical ETR	Virological ETR
IFN + TA1	37.1% (13/35)	37.1% (13/35)
IFN + placebo TA1	16.2% (6/37)	18.9% (7/37)
Placebo (both)	2.7% (1/37)	2.7% (1/37)

Figure 2 shows the mean change in histological activity index (HAI) for the three treatment groups. Overall, 50% of patients treated with IFN/TA1 had a histologic response, defined as a decrease of more than two points in the HAI. Histological responses were seen in 36.3% of IFN-treated patients and 13.9% of placebo-treated patients. Mean improvement in the IFN/TA1 treatment arm was 2.44 points and closely approximated the median improvement of 2.5 points. Patients treated with IFN alone had an average improvement of 1.82 (median, 2). Values in placebo-treated patients were essentially unchanged from baseline, with a 0.03 point worsening of HAI compared with pretreatment values (median, 0).

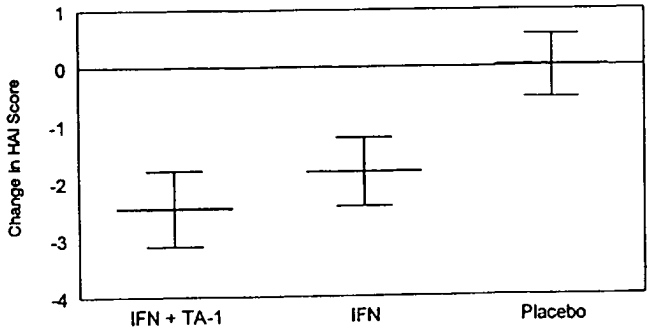

FIG. 2. Change in mean HAI by treatment group. Pretreatment minus posttreatment HAI scores are plotted. Scores were obtained by consensus review of each blinded biopsy result by two hepatopathologists. Intergroup comparison: $P < .05$ for IFN/TA1 vs. placebo only.

Figure 3 shows the mean HCV RNA at timepoints 0, 8, 12 and 24 weeks during treatment. The plots show that the largest reduction in HCVRNA occurred in the IFN/TA1 arm between initiation of therapy and the week 8 visit. Patients treated with placebo did not have meaningful change in viral RNA titer over the treatment period. RNA titers of patients treated with IFN alone decreased by almost 25%, but this difference was not significantly different from pretreatment values. In contrast, IFN/TA1 let to a significant decrease in viral titer compared with baseline at all subsequent time points tested. (Scheffe comparison of means, P .05)

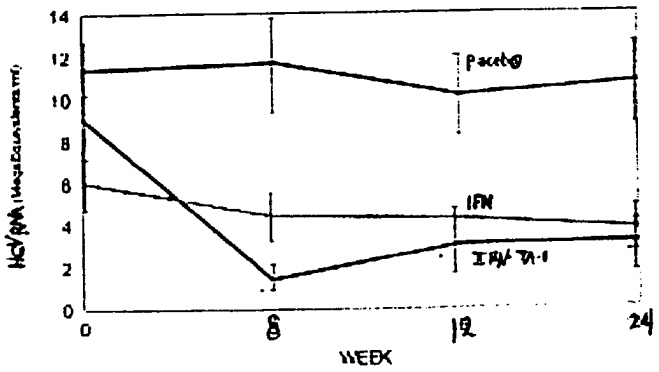

FIG. 3. Sequential mean HCV RNA titer levels. Mean HCV RNA titer levels, determined by the bDNA technique, are shown at weeks 0, 8, 16, and 24. Comparison of HCV RNA titers with baseline levels by group was performed by ANOVA. *$P < .05$.

Table 3 shows side effect findings. There were no significant differences between patients who received combination therapy and those on IFN alone except that nausea and vomiting were somewhat more common in the IFN-alone group.

TABLE 3. Side-Effect Profiles (Intention to Treat)

	Thymosin/IFN	IFN	Placebo	P*
Headache	94.3	89.2	78.4	NS
Fever	62.9	70.3	37.8	.01
Ecchymoses	31.4	29.7	47.2	NS
Fatigue	88.6	97.3	75.7	.02
Depression	60	67.6	54.1	NS
Muscle aches	91.4	89.2	67.6	.01
Pain at injury site	57.1	56.8	40.5	NS
Nausea/vomiting	42.9	70.3	43.2	.03
WBC <3,000	20	13.5	5.4	NS
ANC <1,000	17.1	10.8	0	.04
Platelet <75,000	8.6	8.1	2.7	NS
ANA ≥1:160	8.6	2.7	8.1	NS
ASMA ≥1:160	0	2.7	2.7	NS

NOTE. Data represent percent of patients with side effect.
Abbreviations: WBC, white blood cell count; ANC, Absolute neutrophil count; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody.
*Overall group comparison.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

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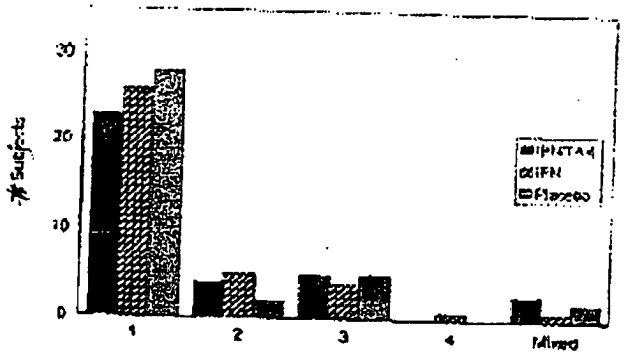

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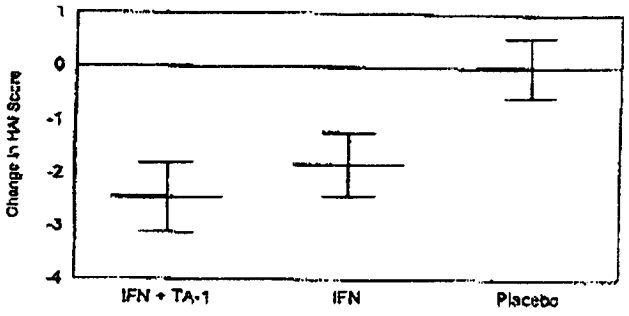

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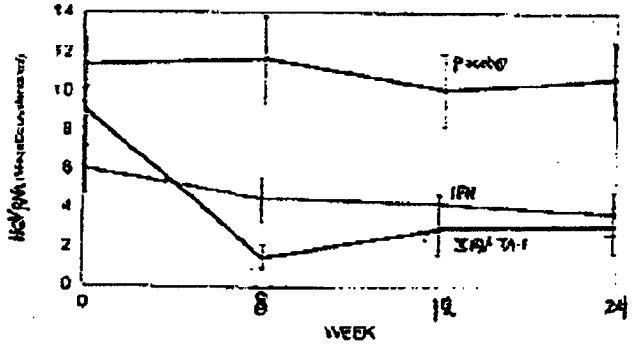

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